REMARKS

With this amendment, claims 1, 4-11, 14-16, 26-27, and 45-48 are pending in the application. Claims 1, 6, 7, 9-11, 14-16, 26, 45, and 48 have been amended. Claims 17-25 and 28-44, drawn to a non-elected invention, and claims 2, 3, 12, and 13 are canceled. The rejections are addressed in the order in which they were presented in the January 3, 2001 Office Action.

Status of the claims

Claims 6, 7, 10, 11, and 48 were amended to recite either moderate hybridization conditions, stringent hybridization conditions, or stringent amplification conditions. This amendment adds no new matter. Support for this amendment can be found, e.g., in the specification on page 24, lines 9-14, and on page 62, lines 5-8.

Claims 1, 14, and 48 have been amended to recite increased "potassium channel current" activity. This amendment adds no new matter. Support for this amendment can be found, e.g., in the specification on page 60, lines 29-30.

Claims 1, 14, 26, and 48 have been amended to delete "functional tetrameric form" and to recite "potassium channel." This amendment adds no new matter. Support for this amendment can be found, e.g., in the specification on page 28, lines 13-18.

Claims 1, 7, 9, and 48 have been amended to delete reference to "SEQ ID NO:3" and "SEQ ID NO:4." This amendment adds no new matter.

Rejection under 35 U.S.C. § 112, second paragraph

"Activity"

Claims 1, 13, 14, 26, and 48 were rejected as allegedly indefinite, as it was not clear to the Examiner what "activity" was increased. Applicants respectfully traverse. However, to expedite prosecution, Applicants have amended the claim to clarify that the "activity" increased is the potassium ion transporting activity, or "potassium channel current" activity, as described in the specification on page 60, lines 29-30. Applicants therefore respectfully request that the rejection with withdrawn.

"Functional tetrameric form"

Claims 1, 13, 14, 26, and 48 were rejected as allegedly indefinite, as it is was not clear to the Examiner what must be combined with the monomer to form the "functional tetrameric form." Applicants respectfully traverse, as this phrase is defined in the specification on page 28, lines 13-18. However, to expedite prosecution, Applicants have amended the claim to delete "functional tetrameric form" and to recite "potassium channel." Applicants therefore respectfully request that the rejection be withdrawn.

"mSlo3 and hSlo3"

Claims 2 and 3 were rejected as allegedly indefinite, as it was not clear to the Examiner what is a mSlo3 or an hSlo3 channel. To expedite prosecution, these claims have been deleted. Applicants therefore respectfully request that the rejection be withdrawn.

Hybridization conditions

Claims 6-7 and 13 were rejected as allegedly indefinite, as the beginning hybridization conditions were not specified, although the end wash conditions were specified. In addition, claims 10-11 were rejected as allegedly indefinite, as the hybridization conditions for an amplification reaction were not specified. Claim 13 has been canceled. To expedite prosecution, claims 6-7, 10-11, and 48 have been amended to recite specific hybridization and wash conditions. Applicants therefore respectfully request that the rejection be withdrawn.

"Molecular weight"

Claim 45 has been rejected as allegedly indefinite for reciting molecular weight values without referring to the method by which the values were measured. Applicants respectfully traverse the rejection for the reasons stated in the Office Action response mailed October 10, 2000. However, to expedite prosecution, claim 45 has been amended to recite the

method by which the values are measured. Applicants therefore respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph: enablement

Claims 1-4, 7, 9-14, 26-27, and 45-48 were rejected as allegedly lacking utility and enablement with respect to the nucleotide sequence of SEQ ID NO:4 and the partial polypeptide that it encodes (SEQ ID NO:3). Applicants respectfully traverse. However, to expedite prosecution, Applicants note that the claims have been amended to delete reference to either SEQ ID NO:3 or SEQ ID NO:4. Applicants therefore respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph: enablement

Claims 1-3, 6-7, 9-14, 26-27, and 45-48 were rejected as allegedly lacking enablement for reciting hybridization under "unspecified hybridization conditions," for reciting hybridization to the nucleic acid of SEQ ID NO:4 , or for reciting binding to antibodies raised against proteins "comprising" SEQ ID NOS:1, 3, 16, or 18.

To expedite prosecution, Applicants have amended the claims to recite specific hybridization and amplification conditions. In addition, the claims have been amended to delete reference to either SEQ ID NO:3 or SEQ ID NO:4 and to recite hybridization to full length nucleotide and amino acid sequences. The claims have also been amended to clarify that the antibodies are raised only against amino acid sequences of SEQ ID NOS:1, 16, or 18, and therefore specifically bind to amino acid sequences of SEQ ID NOS:1, 16, or 18. Finally, the claims have been amended to clarify that the polypeptides have a core domain which has more than 60% identity to amino acids 35-641 of SEQ ID NO:1, rather than having a core domain which has more than 60% identity to a polypeptide "comprising" amino acids 35-641 of SEQ ID NO:1. To the extent that the rejection applies to the claims as amended, Applicants respectfully traverse.

As identified in the Patent Office and the Federal Circuit, whether undue experimentation is required by one skilled in the art to practice to invention is determined by considering factors such as the amount of guidance presented in the application, the state of the prior art, and the presence of working examples. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1985); *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). As described in Wands, a "considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should precede." *Wands*, 8 USPQ2d at 1404 (quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982).

The present invention describes a family of nucleic acids encoding Slo3 monomer proteins which functionally: (1) encode monomers that form potassium channels having a unit conductance of approximately 80-120 pS when the monomer is expressed in a *Xenopus* oocyte; and (2) encode monomers that form potassium channels having increased potassium channel current activity above approximately intracellular pH of 7.1 when the monomer is expressed in a *Xenopus* oocyte; and which structurally either: (1) hybridize to reference full-length Slo3 nucleic acids; (2) are amplified by primers that hybridize to the reference full-length Slo3 nucleic acids; (3) encode monomers having core domains with greater than about 60% homology to a reference Slo3 core domain (amino acids 35-641 of SEQ ID NO:1); or (4) encode polypeptides that bind to polyclonal antibodies raised against reference full-length Slo3 polypeptides.

Hybridization and amplification methods for the identification of nucleic acids are well known to those of skill in molecular biology and are described in the specification, as well as methods of raising specific polyclonal antibodies, and methods of using sequence algorithms for determining percent identity to a given reference sequence. These structural elements therefore provide adequate guidance for routine identification of the nucleic acids of the invention.

Moreover, numerous functional assays to identify Slo3 polypeptides were known to those of skill in the art and described in the specification. For example, the specification describes *Xenopus* oocyte expression to determine the characteristic of unit conductance of

approximately 80-120 pS when the monomer is in a functional tetrameric form of a potassium channel and is expressed in a *Xenopus* oocyte; and the characteristic of increased activity above approximately intracellular pH of 7.1 (*see, e.g.*, Example III). The assays described in the specification, coupled with methodology well known to those of skill in the art, therefore demonstrate that screening for nucleic acids encoding Slo3 proteins having the structural and functional characteristics described above is routine. Therefore, the claimed functional characteristics of the proteins encoded by the claimed nucleic acids would allow one of skill in the art to identify operable embodiments and exclude inoperable embodiments.

Finally, as previously described in the response mailed October 10, 2000, Applicants clearly meet the PTO guidelines for enablement, which set forth the standard for the scope of enablement when a large number of possible embodiments exists. Thus, undue experimentation is not required to practice the claimed invention. Applicants therefore respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph: written description

Claims 1-4, 7, 9-14, 26-27, and 45-48 were rejected as allegedly lacking written description, for claiming polynucleotides encoding (1) polypeptides that bind to antibodies generated against a polypeptide "comprising" an amino acid sequence of SEQ ID NOS:1, 3, 16, or 18; (2) polypeptides having a sequence of SEQ ID NO:3 or encoded by SEQ ID NO:4; (3) polypeptides comprising at least 25 amino acids from SEQ ID NOS:1, 2, 16, and 18, and (4) polypeptides having a core domain that has more than 60% identity to a polypeptide "comprising" amino acids 35-641 of SEQ ID NO:1.

To expedite prosecution, Applicants have amended the claims as follows: (1) Claim 1 now recites antibodies raised against an amino acid sequence of SEQ ID NOS:1, 16, or 18, rather than antibodies raised against a polypeptide "comprising" an amino acid sequence of SEQ ID NOS:1, 3, 16, or 18; (2) Reference to SEQ ID NOS:3 and 4 has been deleted from the claims; (3) Claim 12, reciting fragments of at least 25 amino acids from SEQ ID NOS:1, 3, 16, and 18, has been canceled; and (4) Claim 14 now recites polypeptides that have a core domain

which has more than 60% identity to amino acids 35-641 of SEQ ID NO:1, rather than polypeptides having a core domain which has more than 60% identity to a polypeptide "comprising" amino acids 35-641 of SEQ ID NO:1. However, to the extent that the rejection applies to the claims as amended, Applicants respectfully traverse

The claims fully comply with the requirements for written description of a chemical genus as set forth in *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). As described by the Federal Circuit in *Lilly*, "[a] description of a genus of cDNAs may be achieved by means of . . . a recitation of structural features common to the members of the genus . . . ." *Lilly*, 43 USPQ2d at 1406. Furthermore, the court in *Fiers v. Revel* stated that an adequate written description "requires a precise definition, such as by structure, formula, chemical name, or physical properties." *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). The claims of the instant application set forth both functional elements as well as structural elements, e.g., hybridization conditions, reference sequences to which members of the claimed genus hybridize, reference sequences to which specifically binding antibodies are raised, and reference sequences to which the claimed sequences have a specified percent identity. Therefore, the claimed sequences are thereby defined via shared physical and structural properties.

The present invention describes a family of nucleic acids encoding Slo3 monomer proteins which functionally: (1) encode monomers that form potassium channels having a unit conductance of approximately 80-120 pS when the monomer is expressed in a *Xenopus* oocyte; and (2) encode monomers that form potassium channels having increased activity above approximately intracellular pH of 7.1 when the monomer is expressed in a *Xenopus* oocyte; and which structurally either: (1) hybridize to reference full-length Slo3 nucleic acids; (2) are amplified by primers that hybridize to the reference full-length Slo3 nucleic acids; (3) encode monomers having core domains with greater than about 60% homology to a reference Slo3 core domain (amino acids 35-641 of SEQ ID NO:1); or (4) encode polypeptides that bind to polyclonal antibodies raised against reference full-length Slo3 polypeptides.

The ability of a particular nucleic acid to hybridize under *given conditions* to a reference nucleic acid is a physical/structural property of the nucleic acid, because it relies upon the nucleotide sequence of the molecule (*see, e.g.*, Sambrook, *Molecular Cloning: A Laboratory Manual*, pp. 9.47-9.51 (2nd ed. 1989); *see also* Stryer, *Biochemistry*, pp. 573 (2nd ed. 1975)). As described in Stryer, the transition between hybridization and melting of complementary nucleic acid strands is abrupt and largely sequence dependent. When the temperature of hybridization is provided, one of skill in the art would be able to predict whether or not a given sequence would hybridize to a reference sequence (*see, e.g.*, equations provided in Sambrook, *supra*). Moreover, in the same light, the percent identity of a nucleic acid to a reference sequence is a structural feature, as it relies entirely on the sequence of the molecule. Similarly, the ability of a polyclonal antibody raised against a reference sequence to specifically bind to another polypeptide is a structural feature.

In the present application, Applicants have therefore provided both reference nucleotide sequences, as well as hybridization conditions and sequence analysis algorithms. As required by the standard set forth in *University of California v. Eli Lilly*, these structural features are common to all of the members of the claimed polypeptide genus. The conserved sequences encoding structural features of the genus, and the given conditions under which the claimed genus would hybridize to such reference sequences, bind to antibodies raise dagainst such reference sequences, or have a specified identity to such reference sequences "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (*see*, Office Action, page 4, *quoting Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 111, 1116 (Fed. Cir. 1991)). Applicants therefore respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (twice amended) An isolated nucleic acid encoding a polypeptide monomer of a pH sensitive potassium channel, the monomer:

(i) forming a potassium channel having a unit conductance of approximately 80-120 pS [when the monomer is in a functional tetrameric form of a potassium channel and is expressed in a *Xenopus* oocyte;

(ii)] and having increased potassium channel current activity above approximately intracellular pH of 7.1, when the monomer is expressed in a *Xenopus* oocyte; and

[(iii)] (ii) specifically binding to polyclonal antibodies generated against [a polypeptide comprising] an amino acid sequence of SEQ ID NO:1, [SEQ ID NO:3,] SEQ ID NO:16, or SEQ ID NO:18.

6. (twice amended) An isolated nucleic acid of claim 1, wherein the nucleic acid selectively hybridizes under moderate stringency hybridization conditions[, which end with a wash step at 45°C in a solution comprising 1x SSC ,] to a nucleic acid comprising a nucleotide sequence of SEQ ID NO:2, wherein the hybridization reaction is incubated at 37°C in a solution comprising 40% formamide, 1 M NaCl, and 1% SDS and washed at 45°C in a solution comprising 1x SSC.

7. (twice amended) An isolated nucleic acid of claim 1, wherein the nucleic acid selectively hybridizes under moderate stringency hybridization conditions[, which end with a wash step at 45°C in a solution comprising 1x SSC,] to a nucleic acid comprising a nucleotide sequence of [SEQ ID NO:4,] SEQ ID NO:17, or SEQ ID NO:19 , wherein the hybridization reaction is incubated at 37°C in a solution comprising 40% formamide, 1 M NaCl, and 1% SDS and washed at 45°C in a solution comprising 1x SSC.

9. (once amended) An isolated nucleic acid sequence of claim 1, wherein the nucleic acid has a nucleotide sequence of [SEQ ID NO:4,] SEQ ID NO:17, or SEQ ID NO:19.

10. (once amended) An isolated nucleic acid of claim 1, wherein the nucleic acid is amplified by primers that selectively hybridize under stringent hybridization conditions to the same sequence as the primer sets selected from the group consisting of:

CTCGAACTCCCTAAAATCTTACAGAT (SEQ ID NO:8) and
TTCCGTTGAGCCAGGGGTCACCAGAATT (SEQ ID NO:9);
TCTGCTTTGTGAAGCTAAATCT (SEQ ID NO:10) and
TTTCAAAGCCTCTTTAGCGGTAA (SEQ ID NO:11); and
TTATGCCTGGATCTGCACTCTACATG (SEQ ID NO:12) and
ATAGTTTCCGTCTACTACCGAAA (SEQ ID NO:13);

wherein the amplification reaction comprises an annealing temperature of 50°C for 30 seconds and an extension time of 30 seconds at 72°C for 40 cycles.

11. (once amended) An isolated nucleic acid of claim 1, wherein the nucleic acid is amplified by primers that selectively hybridize under stringent hybridization conditions to the same sequence as the primer sets selected from the group consisting of:

GGCAGCGCTCATTCTTTCCTCCTT (SEQ ID NO:14) and
TGCCCAAAACCTCAACCCAAAATA (SEQ ID NO:15);

wherein the amplification reaction comprises an annealing temperature of 50°C for 30 seconds and an extension time of 30 seconds at 72°C for 40 cycles.

14. (twice amended) An isolated nucleic acid encoding a polypeptide monomer of a pH sensitive potassium channel, the monomer:

(i) having a core domain that has greater than 60% amino acid sequence identity to [a polypeptide comprising] amino acids 35-641 of SEQ ID NO:1 as measured using a sequence comparison algorithm; and

(ii) forming potassium channel having a unit conductance of approximately 80-120 pS [when the monomer is in a functional tetrameric form of a potassium channel and is expressed in a *Xenopus* oocyte;] and

[(iii)] having increased potassium channel current activity above approximately intracellular pH of 7.1, when the monomer is expressed in a *Xenopus* oocyte.

15. (once amended) An isolated nucleic acid of claim 14, wherein the [Slo3] nucleic acid [has] encodes a sequence of SEQ ID NO:1.

16. (once amended) An isolated nucleic acid of claim 14, wherein the [Slo3] nucleic acid [has] encodes a sequence of SEQ ID NO:16 or SEQ ID NO:18.

26. (twice amended) An expression vector comprising a nucleic acid of claim 1[encoding a polypeptide monomer of a pH sensitive potassium channel, the monomer:

(i) having a unit conductance of approximately 80-120 pS when the monomer is in a functional tetrameric form of a potassium channel and is expressed in a *Xenopus* oocyte;

(ii) having increased activity above approximately intracellular pH of 7.1; and

(iii) specifically binding to polyclonal antibodies generated against a polypeptide comprising an amino acid sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:16, or SEQ ID NO:18].

45. (once amended) The nucleic acid of claim 1, wherein the nucleic acid encodes a polypeptide monomer having a calculated molecular weight of between 120-156 kDa, the molecular weight calculated from amino acid sequence.

48. (once amended) An isolated nucleic acid encoding a polypeptide monomer of a pH sensitive potassium channel, the monomer:

[(i)] forming a potassium channel having a unit conductance of approximately 80-120 pS [when the monomer is in a functional tetrameric form of a potassium channel and is expressed in a *Xenopus* oocyte; and

(ii)] and having increased potassium channel current activity above approximately intracellular pH of 7.1, when the monomer is expressed in a *Xenopus* oocyte; wherein said nucleic acid selectively hybridizes under highly stringent hybridization conditions[, which end with a wash step at 65°C in a solution comprising 0.2x SSC and 0.1% SDS,] to a nucleic acid comprising a nucleotide sequence of SEQ ID NO:2, [SEQ ID NO:4,] SEQ ID NO:17, SEQ ID NO:19, wherein the hybridization reaction is incubated at 42°C in a solution comprising 50% formamide, 5x SSC, and 1% SDS and washed at 65°C in a solution comprising 0.2x SSC and 0.1% SDS.